Food and Drug Administration
Center for Drug Evaluation and Research

SUMMARY MINUTES
ARTHRITIS ADVISORY COMMITTEE

August 7, 1998
Holiday Inn Bethesda
8120 Wisconsin Avenue, Bethesda, MD

Members Present
Michelle Petri M.D., M.P.H.,Chair
Steven B. Abramson, M.D.
Barbara C. Tilley, Ph.D.
Leona Malone, MSW
Frank Pucino, Jr., Pharm.D.
E. Nigel Harris, M.D.
Matthew Liang, M.D., M.P.H.

Consultants
Kenneth Brandt, M.D.
David Felson, M.D., M.P.H.
Barbara White, M.D.

Members Absent
David Yocum, M.D.
Daniel Lovell, M.D., M.P.H.
Lee Simon, M.D.
Harvinder Luthra, M.D.

Executive Secretary
Kathleen R. Reedy

FDA Participants
Robert DeLap, M.D.
John Hyde, M.D.
Kent Johnson, M.D.
Laura Lu, Ph.D.
Asoke Mukherjee, Ph.D.
Veneeta Tandon, Ph.D.

Guest Experts
Richard Miller, Ph.D.
Harold E. Paulus, M.D.

These summary minutes for the August 7, 1998 meeting of the Arthritis Advisory Committee were approved on 6/4/99.

I certify that I attended the August 7, 1998 meeting of the Arthritis Advisory Committee and that these minutes accurately reflect what transpired.

Kathleen R. Reedy
Kathleen R. Reedy,
Executive Secretary

Michelle Petri
Michelle A. Petri, M.D., M.P.H.
Chairperson

The Arthritis Advisory Committee met on August 7, 1998 at the Holiday Inn Bethesda, 8120 Wisconsin Avenue, Bethesda, MD to discuss NDA 20-905, leflunomide, Hoechst Marion Roussel. Arava™ was the proposed name which had not yet been approved. The committee had been provided a briefing document from the sponsor and the agency as background approximately 22 days before the meeting. There were approximately 300 people in attendance.

The meeting was called to order at 8:00 by Michelle Petri, M.D., Chair of the Arthritis Advisory Committee. The Meeting Statement was read by Kathleen Reedy, Executive Secretary of the Arthritis Advisory Committee. The Committee introduced themselves as did the guest experts, Harold E. Paulus, M.D., Professor of Medicine at the University of California at Los Angeles and Richard Miller, Ph.D., Professor of Obstetrics, Gynecology and Environmental Medicine at the University of Rochester Medical Center, an expert in teratology.

At 8:30 the Hoechst Marion Roussel, Inc. Presentation began and consisted of:

Introduction: Elaine Waller, Pharm.D.
Vice President, North American Drug Regulatory Affairs, HMR
Preclinical/Pharmacokinetics: Mark Eller, Ph.D.
Senior Director, Biodynamics, HMR
Clinical Efficacy: Vibeke Strand, M.D., FACP
Clinical Associate Professor, Division of Immunology
Stanford University
Clinical Safety: Iris Loew-Friedrich, M.D., Vice President
Product Realization, Head of Global Clinical Management, HMR
Clinical Comment: Marc Hochberg, M.D., Professor of Medicine
Head of the Division for Rheumatology and Clinical Immunology
University of Maryland
Concluding Remarks: Elaine Waller, Pharm.D.

Discussion ensued and after a break, at approximately 11:00, the FDA Presentation began which consisted of:

Medical: Kent Johnson, M.D., Medical Officer
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drugs
Statistics: Laura Lu, Ph.D., Division of Biometrics IV,
Office of Epidemiology and Biostatistics
Pharmacology: Asoke Mukherjee, Ph.D.,
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drugs
Pharmacokinetics: Veneeta Tandon, Ph.D.,
Division of Pharmaceutical Evaluation III ,
Office of Clinical Pharmacology and Biopharmaceutics
with an addendum by Dennis Bashaw, Pharm.D.

There were no registered speakers nor any present for the Open Public Hearing.

After lunch the meeting resumed at 1:45 with Discussion and Questions. There was a great deal of discussion of questions #4 and #5 in which Dr. Miller and the teratologist consultant for the sponsor, Dr. Brent participated.

1. Should leflunomide be approved for relief of signs and symptoms of rheumatoid arthritis? Yes: 10
2. Should leflunomide be approved for retardation of structural damage in rheumatoid arthritis? Yes: 10
3. Should leflunomide be approved at this point for prevention of disability? Wording changed to "improvement of Physical function" and discussion took place around the fact that improvement was shown in one year trials and the Guidance Document asks for two year data. No vote was taken.
4. Does the risk of the use of leflunomide in pregnant women clearly outweigh any possible benefit? Yes: 10 and unamimous agreement that the drug not ever be used in pregnant women. Recommendation that a registry be established for pregnancy in women who had used this drug.
5. What advice should be given to a woman who has been taking leflunomide and wishes to become pregnant, or for a man taking leflunomide who wishes to become a father?

Unanimous (10 yes) agreement that women should have an undetectable blood level (<0.02/mcg/ml) tested twice some time apart.
For men, no change in medication: Yes: 8, No: 1, Abstain: 1.

6. What information should be provided about the risk of liver toxicity? What type and frequency of monitoring should be recommended? How should treatment be modified based on monitoring?

Unanimous support for the monitoring the sponsor followed in the trials: liver function test at 4-8 wk intervals; a sustained elevated ALT <3X, reduce dose of leflunomide, >3X, discontinue drug.

7. What should be advised about the use of leflunomide in patients with hepatic insufficiency or other liver disease?

Unanimous support of the ACR Criteria for laboratory monitoring of patients with hepatic insufficiency which sponsor followed in trials. Agreement for exclusion of patients with liver disease.

8. What information should be provided about the risk of malignancy?

Agreement that the most recent data of follow up be included in the labeling; i.e. malignancy incidence per 100 pt/yr and update regularly.

9. Are additional clinical studies needed to further evaluate leflunomide efficacy and/or safety in rheumatoid arthritis? If so, what studies are recommended?

combination therapy; co-use of methotrexate and leflunomide
long term follow-up information
pediatric trials (polyarticular JRA/normal) open label safety PK
psoriatic arthritis
interaction with uridine, rescue, (reduce risk in pregnancy)

pregnancy registry
tissue concentrations (synovial, seminal fluid)
broadened metabolism studies
ethnic populations, genetic effect
correlation data with radiographic outcomes
extension studies, 2nd year and beyond

The meeting was adjourned at 4:00 pm.

Kathleen Reedy, Executive Secretary
Arthritis Advisory Committee